

Therapeutic Role of Resveratrol and Piceatannol in Disease Prevention

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Abstract

Resveratrol, (3,4',5-trihydroxystilbene) has long been suspected to show a broad range of biological activities of medicinal interest such as anticancer, anti-oxidative, anti-diabetic, anti-aging and anti-inflammatory activities. Piceatannol (3,3',4',5-tetrahydroxystilbene) is a hydroxylated analogue of resveratrol and it confirms a lot of similar biological activities as shown by resveratrol. Both resveratrol and piceatannol are very important naturally occurring polyphenolic stilbenes, produced by plants in response to fungal infection, mechanical damage, or ultra-violet irradiation. They can be consumed on a daily basis as they show no harmful effects on human body. They play a significant role in improving human health. Compared with resveratrol, piceatannol is a more potent anticancer agent and preferable agent with other biological activities like antioxidant activity. This article reports biological activities of the two important stilbenes: resveratrol and piceatannol and their possible role in disease prevention.

Keywords: Resveratrol; Piceatannol; Polyphenols; Biological activities

Introduction

Polyphenols are abundant micronutrients that complement and add to the functions of antioxidants, vitamins and enzymes as a defense against oxidative stress caused by excess reactive oxygen species. They contain phenolic rings in their structure and are found in different forms in nature. These compounds are classified into different groups on the basis of the number of phenol rings that they contain and structural elements that are attached to these rings (Figure 1) [1,2].

Resveratrol is the most well characterized stilbenes, having a trihydroxystilbene skeleton [3,4]. Piceatannol closely resembles resveratrol in structure [5]. Both piceatannol and resveratrol possess almost similar biological activities like antioxidant, antiproliferative and anti-inflammatory properties [6]. The importance of these compounds in disease prevention has been reviewed here.

Resveratrol

Resveratrol (3,4',5-trihydroxystilbene) is a natural stilbene containing two aromatic rings in its structure. It is a phytoalexin formed

naturally by 72 different plant species, especially pine trees, jackfruit, mulberry, blueberry, cranberry, grape vines and legumes (Figure 2). It is found in large amount in peanuts, soybeans and pomegranates [7-10].

Resveratrol exists in two isomeric forms: cis-resveratrol and trans-resveratrol. The trans form is more stable and potent than the cis form. Molecular structure of resveratrol consists of two aromatic rings that are linked together by a methylene double bond (Figure 3) [8].

All the three hydroxyl groups of resveratrol are responsible for intensive hydrogen-bonding network [10]. Its biological activity is dependent on the presence of intramolecular hydrogen bonding, double bond and number and position of hydroxyl groups [11]. Resveratrol is a fat soluble plant secondary metabolite produced with the help of enzyme stilbene synthetase [12]. It is known to possess good cancer chemo preventive properties [10].

Biological Activities of Resveratrol

Resveratrol has many biological roles and different mechanisms of action [13]. It can inhibit the progression of several diseases, including cardiovascular disease, carcinogenic, neurodegenerative, and prevent aging process. Resveratrol has found to possess anti-inflammatory, antioxidant and antimicrobial properties [9,13].

Resveratrol as an antioxidant

Recognition of resveratrol as a natural antioxidant agent was illustrated by Zini et al. [14,15]. Resveratrol possesses both antioxidant and free radical scavenging activity. It increases the activities of antioxidant enzymes such as glutathione peroxidase, SOD (superoxide

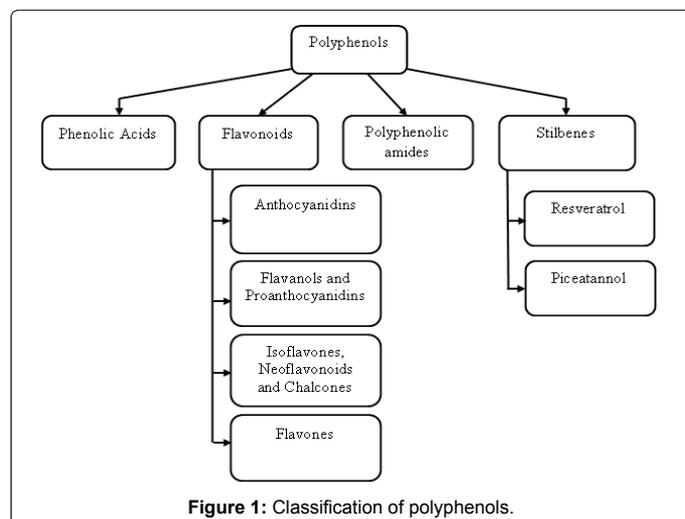


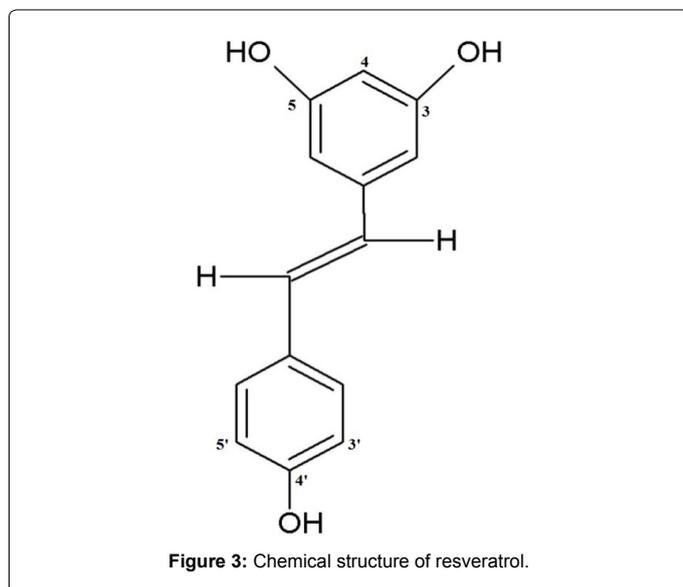
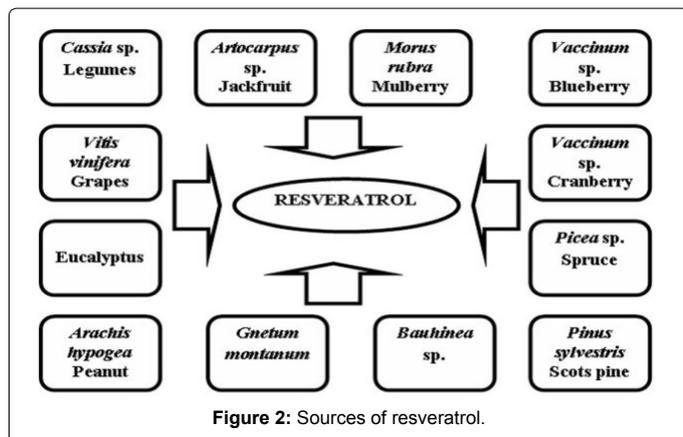
Figure 1: Classification of polyphenols.

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Received September 29, 2014; Accepted November 29, 2014; Published December 05, 2014

Citation: Kukreja A, Wadhwa N, Tiwari A (2014) Therapeutic Role of Resveratrol and Piceatannol in Disease Prevention. J Blood Disorders Transf 5: 240. doi: 10.4172/2155-9864.1000240

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dismutase), catalase, and glutathione reductase [16]. It also maintains the level of intracellular antioxidants in the biological systems [15].

Resveratrol as an anticancer agent

Resveratrol is a good anticancer agent known since ages [11]. It inhibits onset and promotion of cancer. It promotes anti-tumoral activity by inhibiting angiogenesis [17,18]. The anti-cancer effect of resveratrol is associated with the damage of mitochondrial function that leads to an increase in ROS (reactive oxygen species), apoptosis and possibly intracellular drug accumulation via inhibition of proteins involved in MDR (multi-drug resistance) [19].

Resveratrol as an anti-inflammatory agent

Resveratrol exhibits anti-inflammatory activity through modulation of enzymes and pathways that are mostly centered on cyclooxygenases COX-1 and COX-2. It also suppresses the activity of NF- κ B (nuclear factor kappa light chain enhancer of activated B cells) and I- κ B (inhibitor of kappa) kinase and reduced production of prostaglandin E2 (PGE2) and ROS in lipopolysaccharide (LPS)-activated microglial cells [20,21].

Resveratrol as an anti-microbial agent

Resveratrol possesses antimicrobial properties. It inhibits the

growth of some pathogenic microorganism such as gram-positive and gram-negative bacteria and fungi like *Aspergillus niger*, *Helicobacter pylori*, *Aspergillus flavus*, *Candida albicans*, *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* [13]. It inhibits the growth of *Escherichia coli* via site-specific oxidative damage to the cell membrane [14]. Resveratrol is a potent antimicrobial agent and may be used in future for the treatment of infections caused by certain pathogens [22,23].

Resveratrol as an anti-aging agent

Resveratrol possesses anti-aging activity. Its anti-aging activity was seen on yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*) and round worm (*Caenorhabditis elegans*). Resveratrol increases genetic expression of SIR2 enzyme, NAD-dependent, sirutuin class of deacetylase resulting in an increase in the life time of these species [24].

Resveratrol in cardiovascular protection

Resveratrol possesses cardioprotective effects as it inhibits platelet aggregation, thromboxane A2 formation (vasodilator effect) and peroxidase reactions of Cox-1 [25]. It has been observed that even low doses (such as consumed in the common diet) of resveratrol shows cardio-protective activity [26].

Resveratrol in cancer prevention

Resveratrol has been reported to inhibit the proliferation of tumors of breast, colon and prostate cancer. Various mechanisms for the anticancer action of resveratrol include angiogenesis inhibition, cell cycle alteration, apoptosis and antioxidant effects. It also suppresses cytochrome P450 that is considered as procarcinogens [18,25].

Resveratrol in neurological disorder

Resveratrol is a neuroprotective supplement for neurological disorders like Alzheimer's disease, Parkinson disease and Huntingtons disease. It reduces the level of neuronal cell death. It represses p53, thereby preventing neurons from oxidative damage [25].

Resveratrol in thalassemia

Resveratrol possesses both anti-oxidant and HbF (fetal hemoglobin) inducing properties. It activates gamma (γ)-globin genes expression and helps in the production of HbF. This property of resveratrol is helpful in the treatment of beta thalassemia [27].

Resveratrol in diabetes

Resveratrol has been hypothesized to protect β cells in diabetes. It has experimentally proved that resveratrol lowers the insulin secretion in blood. Its inhibitory effect has been proved in hyperinsulinemic animals [28]. Resveratrol shields against hepatic and renal impairment in the diabetic patients [29]. This indicates that resveratrol has beneficial role in the prevention and treatment of diabetes [28].

Piceatannol

Piceatannol (3,3',4',5'-tetrahydroxystilbene) is a naturally occurring hydroxylated analog of resveratrol (Figure 4). It has two phenol rings that are linked together by a styrene double bond. It exists in two isomeric forms: cis- piceatannol and trans- piceatannol. Usually, its trans isomeric form is more stable as compared to cis form [6,30,31].

It has been identified in various plants specifically in passion fruit (*Passiflora edulis*), *Cassia marginata*, *Melaleuca leucadendron*,

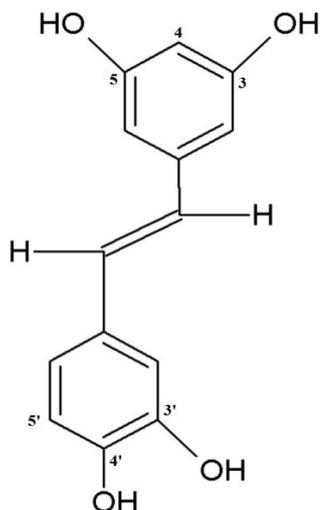


Figure 4: Chemical structure of piceatannol.

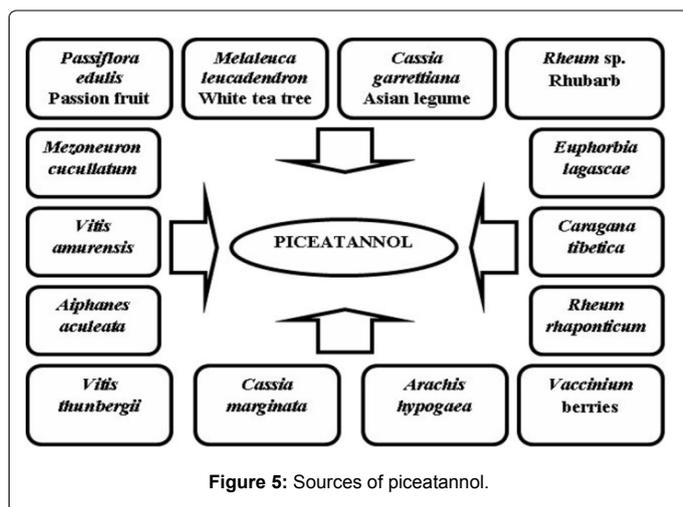


Figure 5: Sources of piceatannol.

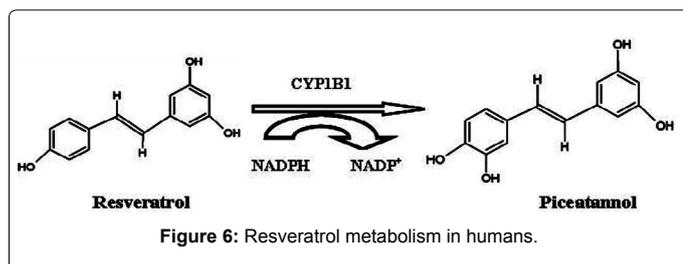


Figure 6: Resveratrol metabolism in humans.

Asian legume (*Cassia garrettiana*), Rhubarb (*Rheum* spp.), *Euphorbia lagascae*, *Mezzoneuron cucullatum*, *Vitis amurensis*, *Caragana tibetica*, *Rheum rhaponticum*, *Partneocissus tricuspidata*, *Aphanes aculeata*, *Arachis hypogaea*, *Vitis thunbergii*, *Ampelopsis brevipedunculata* and *Vaccinium berries* (Figure 5) [6].

Rhodomyrtus tomentosa also known as Sim fruit has been reported to contain 1000-2000 times higher piceatannol than that found in red grape [32]. In humans, resveratrol metabolism in the presence of enzyme CYP1B1 (Cytochrome P450 1B1) produces piceatannol as a major metabolite (Figure 6) [8].

Biological Activities of Piceatannol

Like resveratrol, piceatannol also has many biological roles and different mechanisms of action. It possesses biological activities like anticancer, antioxidant, antileukaemic and anti-inflammatory activities. It also possesses property to combat diseases like breast cancer, prostate cancer, colon cancer, leukemia, lymphoma and melanoma [6].

Piceatannol as an antioxidant agent

The antioxidant activity of piceatannol is due to hydroxyl groups in its stilbene rings. It has good lipid peroxy radical scavenging activity. Semiquinone radical of piceatannol is found to be more stable. Its antioxidant activity was proved by its ability to suppress the production of melanin in B16 melanoma cells [6,33].

Piceatannol as an anticancer agent

Piceatannol exhibits anticancer activity due to its potential to inhibit spread of a vast array of different tumor cells, including lymphoma, leukaemia, breast cancer, prostate cancer, and colon cancer. It shows growth inhibition and the proapoptotic effect on cancer cells. Its proapoptotic effect may be due to loss of mitochondrial potential, activation of caspases and release of cytochrome C [6].

Its proapoptotic activity has been observed in various cancer cells including skin, prostate, bladder and breast. It possesses cytotoxicity activity against prostate cancer cells. It inhibits JAK1 (Janus kinase) activity proving itself to be curative agent for prostate cancer [6]. In colon and liver cancer, piceatannol has found to be responsible for accumulation of cells in G1 and S phase of cell cycle [34]. In bladder cancer, it has been reported that piceatannol induces apoptosis and obstructs G0/G1 cells progression [35].

Piceatannol as an antileukaemic agent

Piceatannol exhibits antileukaemic activity as its treatment results in an increase in Fas and FasL protein expression. It induces death of human leukaemia cells by increasing intracellular Ca²⁺ concentration, activating p38 mitogen activated protein kinase (MAPK), inactivating extracellular regulated kinase (ERK), producing t-Bid and degrading procaspase-8 in leukaemic cells [6,36].

Piceatannol results in apoptosis, DNA fragmentation, decreased Bcl-2 and cIAP-2 (anti-apoptotic proteins) expression and halt of cells in sub G1 phase. Up-regulation of Fas/FasL has been reported in piceatannol treated leukaemic cells [5,37].

Piceatannol as an anti-inflammatory agent

Piceatannol shows anti-allergic inflammatory activity by regulating MAPK signaling pathway. It suppresses SyK activity by obstructing FcεR I-mediated signaling in mast cells [6,38].

Piceatannol as an anti-adipogenic agent

Piceatannol plays a vital role in inhibiting adipogenesis. It downregulates C/EBP and PPAR (pro-adipogenic transcription factors) expression. It also inhibits phosphorylation and kinase activity of signaling pathways including IR and PI3K/Akt pathway [39].

Piceatannol as an antimelanogenic agent

Piceatannol upregulates intracellular GSH level and downregulates GSSG level in B16 cells. It increases GSH/GSSG ratio resulting in an increase in intracellular reducing power, which plays a pivotal role in the regulation of melanogenesis. It lowers melanin content without exhibiting any antagonist effect on cell viability [40].

Activity	Resveratrol	Piceatannol
Antioxidant	Present	Present
Anti-inflammatory	Present	Present
Anticancer	Present	Present
Antileukaemic	Present	Present

Table 1: Similar biological activities of resveratrol and piceatannol [11,14-19,29,32,33,36].

Compound	Position on the ring						
		3	4	5	3'	4'	5'
	Resveratrol	OH	-	OH	-	OH	-
Piceatannol	OH	-	OH	OH	OH	-	

Table 2: Table showing hydroxyl group positions in resveratrol and piceatannol [6].

Parameters	Piceatannol	Resveratrol
Nomenclature	3,3',4',5-trans-trihydroxystilbene	3,4',5-trans-trihydroxystilbene
Spectrophotometric analysis in ethanol	Absorbs maximally at 322 nm	Absorbs maximally at 308 nm.
Content in grapes	About 4-times lower than resveratrol	about 4-times higher than piceatannol
Inhibitory activity	Does not inhibit CYP2E1 (Cytochrome P450 2E1)	Inhibits CYP2E1 (Cytochrome P450 2E1)
Scavenging activity	Show stronger activity to scavenge free radicals. Higher rate constant of reaction with linoleate (LOO•) Concentration of piceatannol required to scavenge O ₂ ⁻ is 1200 times lower than that of Resveratrol	Lower rate constant of reaction with linoleate (LOO•)
Substrate of enzyme catechol-O-methyltransferase (COMT)	Substrate of enzyme catechol-O-methyltransferase (COMT) due to presence of extra 3'-OH group	Not a substrate of enzyme catechol-O-methyltransferase (COMT)
Inhibition of MRP1-mediated transport of 2',7'-bis-(carboxypropyl)-5(6)-carboxyfluorescein (BCPCF) from human erythrocytes	Show moderate activity	Ineffective
Homeostatic effect	Piceatannol-induced homeostatic response has been reported	Not reported till now
TPA-induced NFκB DNA binding	Inhibits NFκB DNA binding to a greater extent	inhibits NFκB DNA binding to a lesser extent

Table 3: Table showing distinction between piceatannol and resveratrol [6,15,18,25].

Piceatannol in diabetes

Piceatannol exhibits antidiabetic phytochemical activity. It enhances glucose uptake, AMPK phosphorylation and glucose transporter 4 (GLUT4) translocation to overcome insulin resistance in diabetic cells. Therefore, it plays a therapeutic role in the prevention of type 2 diabetes [6,41].

Piceatannol in asthma

Piceatannol, a Syk-selective tyrosine kinase possesses significant inhibitory effect in the release of histamine and peptidoleukotriene from sensitized lung fragments. Syk kinase is an essential upstream signaling molecule which activates various inflammatory cells like T cells, B cells and monocytes. Its inhibition in inflammatory cell may prove to be beneficial in the treatment of asthma [42,43].

Piceatannol in bone formation

Piceatannol induces differentiation of osteoblasts from its progenitor stage to well differentiated osteoblasts. It induces BMP-2 (bone morphogenetic protein-2) expression which increases alkaline phosphatase and osteocalcin production in the cells. Piceatannol stimulates BMP2-BMP receptor interaction which is linked with the production of BMP-2. Therefore, piceatannol may be useful in stimulating osteoblastic activity, which results in bone formation [44].

Biological spectrum of piceatannol and resveratrol

Piceatannol and resveratrol both belong to stilbene family. They both can be synthesized by using Perkin's approach, using 3,5-dihydroxyacetophenone as a starting material [45]. They share almost same biological activities such as antioxidant, anti-inflammatory, anticancer and antileukaemic activities (Table 1) [6].

Piceatannol in Alzheimer

Alzheimer's disease is prevalent neurodegenerative disease in the elderly people, which eventually lead to death of person suffering from this disease. Studies have shown a relationship between the consumption of polyphenol rich foods or drinks and the prevention of Alzheimer's disease. The results of a recent study provides evidence that piceatannol have high potential to prevent Alzheimer's disease [46].

Piceatannol in Cardiovascular Diseases

The frequency of cardiovascular diseases is high in developing and developed countries. Cardiovascular diseases are responsible for high rate of mortality. Many drugs are available for treating cardiovascular diseases and complications associated with it. Intake of functional foods or dietary supplements for treating cardiovascular diseases has gained wide acceptance by the general public. Piceatannol is believed to be effective in preventing cardiovascular diseases such as arrhythmia, hypercholesterolemia, angiogenesis and atherosclerosis [47].

Pretreatment with piceatannol suppresses cardiac hypertrophy which has been assessed by expression level of hypertrophy markers, cross-sectional area and heart weight/body weight ratio. It also inhibits cardiac hypertrophy induced by lentiviral GATA-6 [48].

Piceatannol in reducing toxic effect of neutrophils

Piceatannol has ability to reduce the toxic effect produced by neutrophils. It elevates the percentage of early apoptotic neutrophils and hinders the activity of protein kinase C which is the main regulatory enzyme in neutrophils. The result indicates that piceatannol may be used as a complementary medicine in lowering the level of activated neutrophils [49].

Comparative Biological Properties of Piceatannol and Resveratrol

Piceatannol is a more active resveratrol analogue due to the presence of additional hydroxyl group at 3' position (Table 2). It possesses stronger anticancer activity than resveratrol [6]. Piceatannol possesses higher ability to scavenge free radicals as compared to resveratrol [50]. The presence of an extra hydroxyl group in piceatannol makes it reactive and more potent antioxidant as compared to resveratrol. The required concentration of piceatannol to scavenge free radicals is 1200 times lesser than that of resveratrol [6].

Although, resveratrol possesses several beneficial effects on human health as well as in preclusion of many chronic diseases, but its low

bioavailability and rapid metabolism limits its use in the preclusion of chronic diseases [8]. Table 3 illustrates dissimilarity between resveratrol and piceatannol.

Piceatannol has much more effective biological activity and bioavailability as compared to resveratrol. Therefore, piceatannol is gaining more scientific attention than resveratrol for improving health related diseases. But more studies are needed to prove its effective diseases saving properties [8,38].

Conclusions

Resveratrol and piceatannol are naturally occurring polyphenolic compounds with a wide range of biological activities. Resveratrol plays a significant role in prevention of diseases, but due to its fast metabolism in the body and poor bioavailability, it is less preferred. Piceatannol being a natural analogue of resveratrol, contains additional hydroxyl group which confers to its more effective biological activities as compared to resveratrol. In order to make both of these compounds applicable for clinical use, they should be studied more extensively to understand their bioavailability, metabolic pathways and toxicity in humans.

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